Cost of Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infection Management in Young Children at the Regional and Global Level

Cost of RSV-associated ALRI management in young children at the regional and global level - A systematic review and meta-analysis

Running title: RSV management cost in young children

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Abstract:

Respiratory syncytial virus (RSV) is a major cause of acute lower respiratory infection (ALRI) in young children aged <5 years. We aimed to identify the global inpatient and outpatient cost of management of RSV-ALRI in young children to assist health policy makers in making decisions related to resource allocation for interventions to reduce severe morbidity and mortality from RSV in this age group. We searched 3 electronic databases including Global Health, Medline and EMBASE for studies reporting cost data on RSV management in children under 60 months from 2000 to 2017. Unpublished data on the management cost of RSV episodes were collected through collaboration with an international working group (RSV GEN) and claim databases. We identified 41 studies reporting data from year 1987 to 2017, mainly from Europe, North Americas and Australia, covering the management of a total of 365,828 RSV disease episodes. The average cost per episode was € 3,452 (95% CI: 3,265 - 3,639) and € 299 (95% CI: 295 – 303) for inpatient and outpatient management without follow-up, and increased to € 8,591(95% CI: 8,489 – 8,692) and € 2,191 (95% CI: 2,190 – 2,192) respectively with follow-up to 2 years after the initial event. Known risk factors (early and late pre-term birth, congenital heart disease (CHD), chronic lung disease (CLD), intensive care unit admission and ventilator use) were associated with € 4,160 (95% CI: 3,237 – 5,082) increased cost of hospitalization. The global cost of inpatient and outpatient RSV ALRI management in young children in 2017 was estimated to be around € 4.82 billion (95%CI: 3.47 – 7.93), 65% of these in developing countries and 55% of global costs accounted for by hospitalization. We have demonstrated that RSV imposed a substantial economic burden on health systems, governments and the society.

Keywords: Respiratory syncytial virus; lower respiratory infection; children; cost of illness; systematic review; meta-analysis

Respiratory syncytial virus (RSV) is recognized as the most frequent cause of acute lower respiratory infections (ALRI) in infants and children below 5 years of age. It is estimated that in 2015 about 3.2 (95%CI: 2.7 – 3.8) million young children worldwide were hospitalized due to RSV-associated ALRI, while 59,600 (48,000 – 74,500) children younger than 5 years died in hospital from RSV globally[1]. The yearly seasonal outbreaks of RSV infections disproportionately affect young children, especially during their first year of life. A broad spectrum of disease presentations is observed, ranging from coughs and colds to severe bronchiolitis and pneumonia necessitating hospitalization. All forms of RSV disease cause a certain degree of burden on the healthcare system, financially as well as logistically.

Currently, there are no licensed RSV vaccines available, but about 20 RSV vaccines and immune-therapeutics are in clinical development[2]. The currently available prophylactic antibodies against RSV (polyclonal RSV-IVIG and monoclonal Palivizumab) are expensive, not widely available and only recommended for patients with a high risk of severe RSV disease[3]. This highlights the need for a global evaluation of management costs related to RSV disease, especially among those groups of patients who are not usually offered prophylaxis. Global cost evaluation would provide a better understanding of the disease impact on society and aid donors and health policy makers in setting priorities for development and introduction of new interventions.

Therefore, we conducted a systematic review of the published literature and assembled unpublished data with the aim of identifying the overall costs related to management of RSV-ALRI episodes by country, classified by type of comorbidity and/or intervention.

Materials and Methods

Published literature: Search Strategy and Selection Criteria

Following the PRISMA guidelines, Medline, EMBASE and Global Health (via the Ovid interface) were searched online to obtain maximum coverage of the published literature. General search headings identified were: Respiratory Syncytial Virus (RSV) and Economics. We focused on studies published between 1st Jan 2000 and 30th September 2017. Final search strategies were checked and approved by an independent librarian to ensure accuracy and validity of the search strategy. Three authors (S.Z.,

B.F., L.Z.) independently screened the titles and abstracts of all records retrieved and checked the reference lists of eligible articles for further studies. We included studies published in English, Spanish, French and Chinese. Any disagreements were arbitrated by H.N. (Supplementary Table 1-3).

We included all studies reporting RSV-related costs in children younger than 60 months. Treatment was provided to infected children according to local standard procedures. All studies documenting novel cost data were considered eligible. The inclusion and exclusion criteria are shown in Supplementary Table 4.

Data Extraction

We collected data, cost per episode, including direct medical, non-medical (transportation and food) and indirect costs (caregivers cost and productivity loss) and on length of stay (LOS) in hospitals. Unit costs for medicines and the utilization of resources were also documented if available. Three researchers (LZA, FB & SZ) extracted these data independently and final results were crosschecked. We designed a costing spreadsheet with detailed descriptions of case definitions and methods used for the data collection. Primary data collection was conducted using standardized templates and guidelines at each individual study site.

Costs were first converted to the local currency, when needed, for the stated price year of the study, and inflated to their 2017 level using the country-specific gross domestic product (GDP) deflator index from the International Monetary Fund (IMF) World Economic Outlook database[4]. Then, all costs were converted to their equivalent price in 2017 $US based on the purchasing power parity of GDP (period average in 2017). Final results were then converted into 2017 € (1 US$ = €0.887397)[5]. Industrialized and developing country designations followed UNICEF categories[6].

Statistical Analysis

The cost data were stratified by WHO region, follow-up and comorbidity status. Cost per episode, cost by component (direct medical, direct non–medical and indirect costs), length of stay and percentage of total costs per episode in each component were summarized. Relative estimates for risk group were obtained from each study.

Based on data generated for each study, meta-analyses of cost per episode and LOS was quantified

using sample size weighted, random effect model of meta-analysis (metan command) in Stata V.12 (StataCorp, College Station, Texas, USA). For each subgroup of RSV management, we summarized the data and reported a point estimate and 95% CI for the cost per episode and the respective LOS. Global costs of RSV management were modeled using recently published estimates for RSV episodes and RSV hospitalizations at global and regional levels in 2015[1]. We then applied these estimates to our unit cost estimates from each WHO region to generate global estimates for RSV-related ALRI in children. We assumed that 90% and 63% of RSV positive cases in high-income and low and middle income countries respectively sought and received appropriate health-care [7]. Meta-estimates for global costs were estimated using Monte Carlo simulation approach using @RISK, version 7.0 (Palisade Corp), as reported by Zimlichman et al.[8]. For each included study, we simulated a distribut with pooled results weighted by sample size. A point estimate of the cost per episode (with SD and 95%CI) in each study was reported based on a Monte Carlo simulation of 100,000 sample draws.

We used cost data from high-income countries for developed country settings. Due to limited RSV outpatient management cost data in low and middle-income countries, we used the cost ratio of pneumonia outpatient management cost between high income and low and middle-income countries[9], and calculated the costs of RSV management in low and middle-income countries reflecting costs for developing countries.

Quality Assessment

All papers were assessed using a modified Drummond Checklist for economic evaluation focusing on the methodological robustness and detail of reporting costs (Supplementary Table 5). Studies with quality score less than 5 (40% of total score) were considered to be of low quality and were excluded in the final analysis.

Results

Search Results

The initial search strategy identified 3,581 references after excluding duplicates and a total of 38

published studies were considered eligible and included in the systematic review [10-47]. Three out of thirteen contacted sites provided additional unpublished data. A total of 41 studies were included in the final review (Figure 1).

Study Characteristics

A total of 365,828 RSV disease episodes were included in the cost analysis, including 338,542 inpatient cases and 27,286 outpatient and emergency cases. The mean sample size of included studies was 8,923 (Range 12-94,252). A complete documentation of the characteristics of each study is summarized in Supplementary Table 6.

Data covered 5 out of 6 WHO regions with no data from the African Region (Supplementary Figure 1). Cost data were obtained from 14 countries, with studies from the United States representing the largest single group (n=18 or 44%). The majority of studies (32 studies) were cost-of-illness studies while the remaining 9 studies were cost-effectiveness studies, with 7 prospective and 34 retrospective studies. The perspective of costing was explicitly stated in 19 (46%) of the studies, with the most common perspective that of a third party payer (i.e. public or private health care insurers). Hospital chart, government and insurance databases were the most common sources for cost data.

The majority of the included studies focused on children under 36 months of age (25 studies). Paediatric patients included general and/or high-risk patients (22 studies). RSV cases were identified by ICD 9 and 10 codes, direct immunofluorescence, indirect RSV antigen detection methods, RT-PCR and viral culture.

Cost reporting dates ranged from 1987 until 2016. Individual studies monitored costs over a mean period of 3.6 years (0.25 to 18 years). Ten studies (24%) were follow-up studies over a designated time period (1 month to 2 years) observing costs during and after initial RSV episodes.

The average quality score was 8.9 points (SD 1.6, range 6,11) with a maximum possible score of 13 (Supplementary Table 6). Most studies failed to report unit costs and the quantity of resources used, or discounting and sensitivity analyses.

Cost per patient for RSV management

The global overall weighted mean cost per outpatient patient ranged from € 57 to € 48,262) (Supplementary Figure 2). Costs for outpatient management (per disease episode) without follow-up (€299) were siginificantly lower compared to outpatient management (€ 2,191) with follow-up (Supplementary Table 1). For inpatient RSV management, mean cost per patient was € 4,712 (95% CI 4,568- 4,856, range € 92 to € -165,602) (Figure 1). Studies with a follow-up period up to 2 years reported higher per patient costs on average (€ 8,591 vs € 3,452). RSV management costs were also higher in high income countries (€ 3,602) compared to middle income countries (€ 925). Cost data from low income countries were unavailable.

At regional level, European Region (EUR) studies accounted for 40.3% of inpatient cases (all in high income countries) and 1.7% of outpatient cases (Supplementary Table 1). Studies from the USA and Canada accounted for 50.8% of the inpatient cases and 98.0% of the outpatient cases. Inpatient management in middle-income countries were mostly reported in studies from the Western Pacific Region (WPR). The weighted mean cost for inpatient management without follow-up was similar in EUR and WPR (€ 1,530 vs € 965), whereas the cost in the USA and Canada was nearly 4-6 times higher (€ 6,315). Inpatient management costs with follow-up in high income countries of EUR, AMR and WPR was € 18,607, € 9,506 and € 4,775 respectively.

Direct and indirect non-medical costs were reported in 7 studies. Direct non-medical costs (mainly food and transportation) were reported to be 2.3-3.8% of the total management cost per patient. Indirect costs representing productivity losses were reported to be 5.8–31.6% of the total management cost (Table 2).

Costs for special risk groups were compared with the costs for healthy full term infants. Children with comorbidities, such as CHD, CLD and BPD, had increased cost for RSV management at € 9,825 (95%CI: 900 - 18,839), €10,879 (95%CI:1,858 - 19,900), € 5,516 (95%CI:2,111 - 8,921) respectively (Table 3). Preterm children cost € 4,695 (95%CI: 3,852 -5,537) more than term children. A single study in Malaysia reported higher costs for preterm infants and children with underlying disease: nearly 12 times the cost for healthy full-term infants. (Supplementary Table 7). ICU care was € 14,809 (11,210 - 18,409) more expensive than non-ICU care (Table 3).

Global cost estimates RSV management

We estimated that the global direct medical costs for management of RSV-ALRI in children aged below 5 years in 2017 was about € 4.82 billion (95% CI: 3.47- 7.93) from the health care payer's perspective, of which nearly 55% were hospitalization costs (€ 2.65 billion, 95% CI: 2.26 -3.28) and outpatient management accounted for the remainder (€2.17 billion, 95% CI: 1.20 -4.65) (Table 4) .This estimate includes the direct medical cost only. Direct non-medical costs and indirect costs would futher add 8.7% and 31.6%, respectively, to the total direct medical costs. The total cost in developing countries, where 92% of cases occured, was € 3.13 billion (95% CI: 2.27 -5.13) , accounting for 65% of the RSV economic burden globally and 2.7 ‰ (95%CI: 0.3‰ – 8.3‰) of the healthcare expenditure in these countries[48].

Discussion

This is the first systematic review and meta-analysis summarising the current evidence related to the cost of RSV disease among children below 5 years of age. It demonstrates that the economic burden associated with RSV disease is substantial. The estimated global costs of RSV-ALRI inpatient and outpatient management from a healthcare payer's perspective was € 4.82 billion (95% CI: 3.47 -7.93) in children younger than 5 years in 2017. Relative to global healthcare expenditure, RSV management costs in children below 5 years old alone accounted for 0.7 ‰ (95% CI: 0.2‰ – 14.7‰) [48].

This study demostrates the level of budget that could be avoided (and made available for other health service needs) if there were prophylactic strategy to prevent many of these episodes. Direct non-medical and indirect costs may further contribute to the financial and social burden on families of children affected by RSV disease. Outpatient follow-up after initial RSV disease episodes may reveal additional costs compared to the analysis restricted to a single clinic visit, but outpatient care may also be effective in preventing additional cost due to re-hospitalization.

The average cost of inpatient hospitalization per patient was highly dependent on the setting. The substantial differences in cost between settings may be due to the overall economic situation as well as different requirements/thresholds for hospitalization. Inpatient cost in middle-income countries was

even higher than the inpatient cost in high-income countries (1.53 billion vs. 1.15 billion). Hospitalization costs accounted for 55% of the all RSV management cost globally and 65% of the total RSV cost generated in developing countries. Meanwhile, the mean cost per inpatient for RSV management exceeded the total healthcare expenditure per capita in most OECD countries [7]. The above evidence indicates that RSV management places a heavy burden on the healthcare system, particularly in developing countries.

The baseline risk status (eg. prematurity) should be documented, as the cost for high risk groups would potentially increase. Hospitalisation costs in children with risk factors (early and late pre-term, CHD and CLD) were substantially higher (1.8-5.9 times) compared to children without such risk factors. This reflects that patients with comorbidities, who, on average, experience more severe RSV infections, typically require prolonged hospital stays and/or ICU admission. It may also be affected by the accessibility to ambulatory and primary care.

Very few studies investigated the indirect costs incurred by parents or families taking care of children with RSV infection. The need to take care of children with RSV may generate a significant additional burden (including financial) on parents and other caregivers. On the one hand, indirect costs may generate more costs to family and society. The indirect cost of RSV management accounted for 20% of the total cost in Bangladesh [46]. The productivity loss per case of RSV in the US was reported as US$2,697-5,439[27]. On the other hand, out-of-pocket payments for RSV management can cause households to incur catastrophic expenditures, which in turn can push them into poverty. The out-of-pocket cost was 24% (range 17%-32%) of monthly household income of affected families in Bangladesh[46]. Without healthcare insurance, over 50% of the studied families obtained loans to meet treatment cost. This was also observed for child pneumonia management in other low-income countries, such as Ethiopia[49]. Coping with considerable costs of RSV management in middle and low income countries can lead to catastrophic consequences and impoverishment for the affected families. More cost studies are needed to better understand the impact and the possible benefits of adequate prevention.

RSV infection may lead to prolonged respiratory morbidity following an initial disease episode. Follow-up studies provided insight into the financial burden generated by prolonged RSV disease. The inpatient costs per admission nearly doubled and the duration of hospital stays increased by 33% in the studies with follow-up. Consequently, reported outpatient costs also increased up to 12-fold compared to a single primary care or emergency room visit. Therefore, outpatient costs of managing RSV infection are likely to be substantial when costs are monitored beyond the acute period. Further studies are required to advance our understanding of the long-term costs and consequences of RSV disease.

This study highlights the broad range of allied costs related to RSV-ALRI (at regional and country levels) due to differences in management styles, cost reporting methods, and access to care in different parts of the world. Regardless of the setting and methodological heterogeneity, our data underline the urgent need for effective means of disease prevention and intervention, i.e. the development of RSV vaccines and therapeutics. The differences in costs reported from different sources and the methodological standardization achieved in this current study provide a useful roadmap for future research, which is urgently needed considering the imminent development of new options for the treatment and prevention of RSV disease.

Several limitations of this meta-analysis should be noted: First, only 14 publications (35%) specified the exact range of costs including mean and median costs, and no data sets were obtained from study authors except unpublished studies. Adequate representation of cost data should always include both a central estimate (ie mean and median) and an associated uncertainty interval (SD, 95% CI or interquartile range) Secondly, the methods for case ascertainment differed significantly from study to study ranging from suspected RSV diagnoses as they were coded in clinical records (ICD-9, ICD-10), to laboratory methods with highly variable sensitivity and specificity. RSV cases may be underreported by using ICD codes. Third, the USA is known to be an outlier in terms of health care costs per case, and therefore not representative for the Americas, or for any other group of countries. The fact that a disproportionately large number of US studies were found (18/41), introduces an upward bias in some

of our summary estimates. Fourth, our results should be interpreted with caution as there are limitations to using meta-analysis in the context of healthcare costs which have significant hetergeneity and are likely context and site specific.. Additionally, the true uncertianity in the results are likely to be much wider than the (narrow) 95%CI reported in our analyses. Finally, due to a lack of data in outpatient settings and in low income countries, the global cost estimate may be further overestimated. In our analysis, data from middle income countries were used as proxy for cost data for developing countries, which may have also contribute to the differences compared to our previous estimates for all-cause pneumonia [50]. This may be further magnified by our assumption of universal coverage of treatment in children with RSV-ALRI. Of note, these reported costs exceed previous estimates on the cost of child pneumonia management - €1.7 (95% CI: 0.6 – 2.8) billion (price year: 2017) from the healthcare perspective [9].

This review provides a first overview of treatment costs related to of RSV disease in different parts of the world. There was an imbalance in geographical representation of the data collected, with no data from South America and Africa and very limited data from South East Asia and the Eastern Mediterranean regions of WHO. Despite this, our study provides a first set of important information on management costs for hospital administrators, public health stakeholders and policy makers, helping them in the allocation of scarce resources and supporting the development of preventive interventions.

Author contributions. H.N. designed the study and superivsed the project. S.Z., L.Z.A., and F.B. collected and analysed the data. B.R., B.S., M.A., M.G.L., L.T.N, A.K. S.T., M.H.K. provided unpublished data. S.Z., L.Z.A., and F.B.wrote the initial draft. H.N., P.B., B.R., and M.H.K. critically revised the intellectual content of the manuscript. All authors reviewed and approved the final draft of manuscript.

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Conflicts of interest statement

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may hold shares/stock options as part of her remuneration package. MHW was an employee of Sanofi Pasteur at the time of the work.

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Table 1 Meta-analysis results of weighted mean hospital LOS per patient and range of mean cost by WHO region and patient group (printed)

WHO Region	Patient Group	Sample Size (% of global sample size)	Weighted Mean LOS (Days) (95%CI)	Range of Mean Cost Per Patient/Episode (Euro€ 2017)
Global	**Inpatient Overall**	337,775 (100%)	3.51 (3.47- 3.55)	79-30,350
	Inpatient without follow-up	244,913 (100%)	3.28 (3.23 -3.34)	79-30,350
	High income countries	240,730 (100%)	3.09 (3.03-3.15)	781-30,350
	Middle income countries	4,183 (100%)	6.41 (6.36-6.46)	79-577
	Inpatient with follow-up	82,859 (100%)	4.2 (4.18-4.21)	419-28,608
	Outpatient Overall	36,286 (100%)	N/A	57-8,691
	Outpatient without follow-up	21670 (100%)	N/A	57-1,029
	High income countries	21625 (100%)	N/A	231-1,029
	Middle income countries	45 (100%)	N/A	57-304
	Outpatient with follow-up	14,616 (100%)	N/A	69-8,691
EUR (10 studies)	**Inpatient Overall**	136,311 (40.3%)	2.68 (2.63 -2.72)	781-25,612
	Inpatient without follow-up*	136,261 (55.6%)	2.67 (2.62 -2.71)	781-6,156
	Inpatient with follow-up	50 (0.6%)	39.8 (33.7 -45.9)**	2,147-25,612
	Outpatient Overall	633 (1.7%)	N/A	87-3,031
	Outpatient without follow-up	633（2.9%）	N/A	87-292
	Outpatient with follow-up	—	N/A	676-3,031
AMR (19 studies)+	**Inpatient Overall**	170,891 (30.8%)	3.96 (3.89 -4.04)	419-30,350
	Inpatient without follow-up*	104,201(42.5%)	3.64 (3.52 – 3.76)	3,022-30,350
	Inpatient with follow-up	66,690 (80.4%)	4.46 (4.44 -4.48)	419-28,608
	Outpatient Overall	35,575 (98.0%)	N/A	69-8,691
	Outpatient without follow-up	20,959 (96.7%)	N/A	117-1,029
	Outpatient with follow-up	14,616 (100%)	N/A	69-8,691
WPR (10 studies)	**Inpatient Overall**	30,067 (4.1%)	4.6 (4.57-4.62)	215-4,921
	Inpatient without follow-up	13,948 (5.6%)	6.43 (6.38-6.49)	215-1,817
	Inpatient with follow-up	16,119 (19.4%)	3.0 (2.99 – 3.01)	4,630-4,921
	Outpatient Overall	57 (0.2%)	N/A	183-304
	Outpatient without follow-up	57(0.2%)	N/A	183-304
	Outpatient with follow-up	-	N/A	-
SEAR (1 study)	**Inpatient without follow-up (Middle income countries)**	39 (0.9%)	4.59 (4.57-4.62)	79-150
	Outpatient Overall	21(0.1%)		57-106
EMR (1 study)	**Inpatient without follow-up (Middle income countries)**	467 (11.1%)	4.27 (4.24-4.30)	577

* All high income countries only; N/A: Not Applicable; EUR: European Region, AMR: Region of The Americas, WPR: Western Pacific Region, SEAR: South East Asia Region; EMR: Eastern Mediterranean Region. **Based on one study only, with 2 years follow-up. + Based on 18 US studies and 1 Canadian study.

Table 2 Percentage of direct non-medical cost and indirect cost in total cost per episode (online)

Patient Group	Author Year	Country	Cost Euro€ 2017 Mean(SD), Mean(95%CI) Median[7]	Percentage
Direct non-medical cost	Ehlken 2005[10]	Germany	129(154)	3.80%
	Leader 2003[27]	USA	241(1,545)	-

	Miedema 2001[11]	Netherlands	75	2.30%
	Rath 2015[25]	Germany	26	0.7%
	Lucero 2015[26]	Philippines	1	0.41%
Indirect cost	Ehlken 2005[10]	Germany	198(366)	5.80%
	Garcia-Marcos 2014[14]	Spain	47(61)	15.90%
	Leader 2003[27]	USA	2,307 – 4,652	-
	Bhuiyan 2017[46]	Bangladesh	31 [18-47]	20.21%
	Miedema 2001[11]	Netherlands	433	13.40%
	Rath 2015[25]	Germany	813-	22.15%-31.64%
	Lucero 2015[26]	Philippines	1,1613(12)-13(34)	1.43%-5.83%

Table 3 Cost differences between high-risk group and low risk groups (online)

Risk Group	WHO Region (Study country, number of studies)	Weighted Cost Difference (95% CI) Euro 2017
Low risk vs. High risk*	Overall	4,160 (3,237 - 5,082)
	EUR (Netherlands, UK, 2)	2,274 (-1,152 - 5,702)
	AMR (USA,8)	9,661 (6,669 - 11,234)
	WPR (Australia, Taiwan China, Malaysia, 5)	2,174 (1,266 - 3,075)
Term children vs. preterm children	Overall	4,695 (3,852 - 5,537)
	EUR (Netherlands, 1)	3,364 (839 - 5,890)
	AMR (USA, 9)	6,626 (5,175 - 8,077)
	WPR (Australia, Malaysia, 3)	3,240 (2,638 - 3,841)
Normal vs. low birth weight (<2500g)	Overall	1,249 (757 - 1,740)
	EUR (Netherlands, 1)	1,320 (789 - 1,850)
	WPR (Australia, 2)	1,247 (113 - 2,383)
Term vs. CHD	Overall	9,825 (900 - 18,839)
	AMR (USA, 4)	12,807 (1,906 - 23,707)
	WPR (Australia, 1)	-775 (-2,352 - -802)
Term vs. CLD	Overall	10,879 (1,858 - 19,900)
	AMR (USA, 4)	12,571 (-2,298 - 27,441)
	WPR (Australia, 1)	4,127 (2,825 - 5,429)
Term vs. BPD	Overall	5,516 (2,111 - 8,921)
	EUR (Netherlands 1)	3,548 (1,118 - 5,978)
	WPR (Australia, 1)	7,049 (6,810 - 7,289)
Non-ICU vs. ICU	Overall	14,809 (11,210 - 18,409)
	AMR (USA, 2)	44,751 (5,437 - 84,067)
	EUR (Germany, 1)	17,750 (13,911 - 21,589)
	WPR (Australia, China, Malaysia, 3)	1,412 (167 - 2,658)

LBW: Low birth weight; CHD: congenital heart disease; CLD: chronic lung disease; BPD: Bronchopulmonary dysplasia; ICU: intensive care unit. * High risk including: preterm, CLD, CHD, LBW, BPD, vulnerable children, multiple underlying diseases, indication for prophylaxis.

Table 4 Global cost estimates for RSV management (online)

Patient Group	RSV management costs in developed countries (Billion € (95% CI))	RSV management costs in developing countries (Billion € (95% CI))	Total Costs (Billion € (95% CI))
Inpatient	1.15 (0.97 – 1.46)	1.53 (1.29 – 1.82)	2.65 (2.26– 3.28)
Outpatient	0.58 (0.23-1.33)	1.60 (0.97 – 3.31)	2.17 (1.20 – 4.65)
Total	1.69 (1.20 – 2.79)	3.13 (2.27- 5.13)	4.82 (3.47 – 7.93)

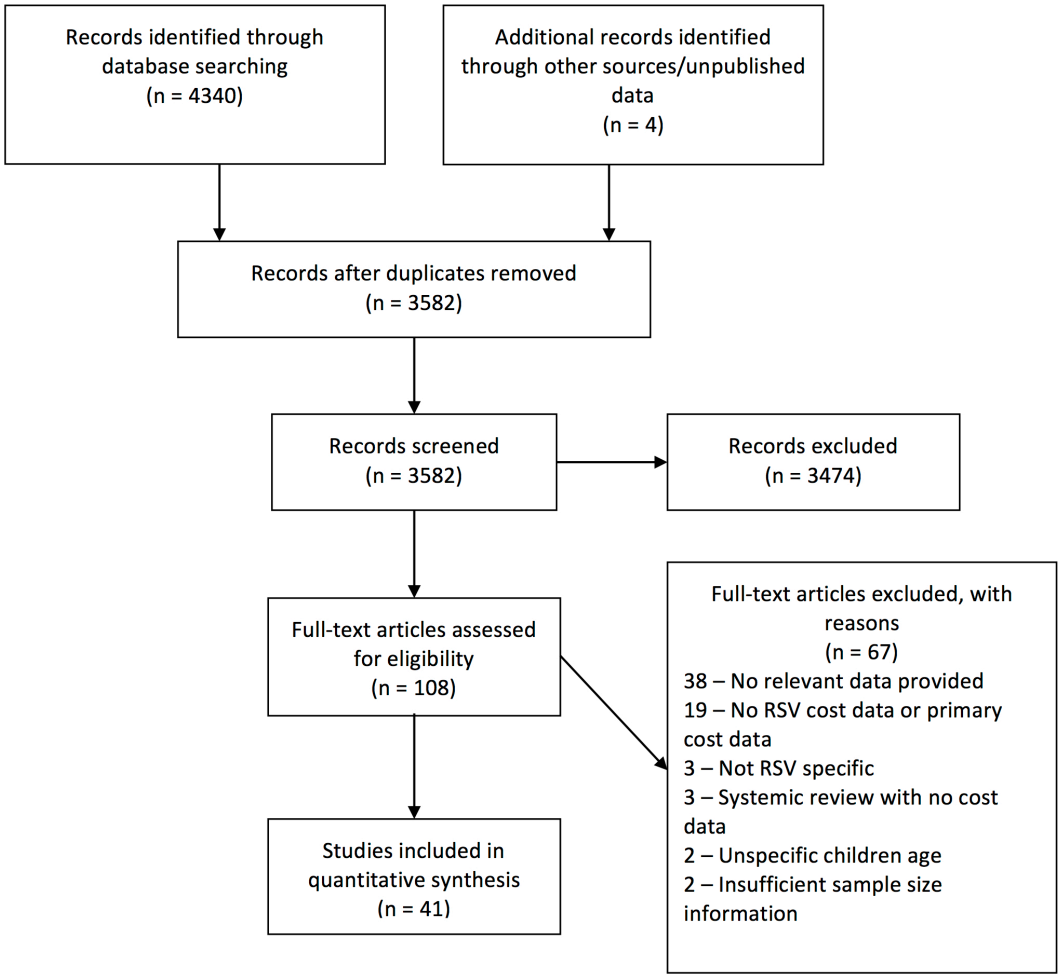

Figure 1. *Overview of Search Results*

Figure 1. Overview of Search Results (Online)

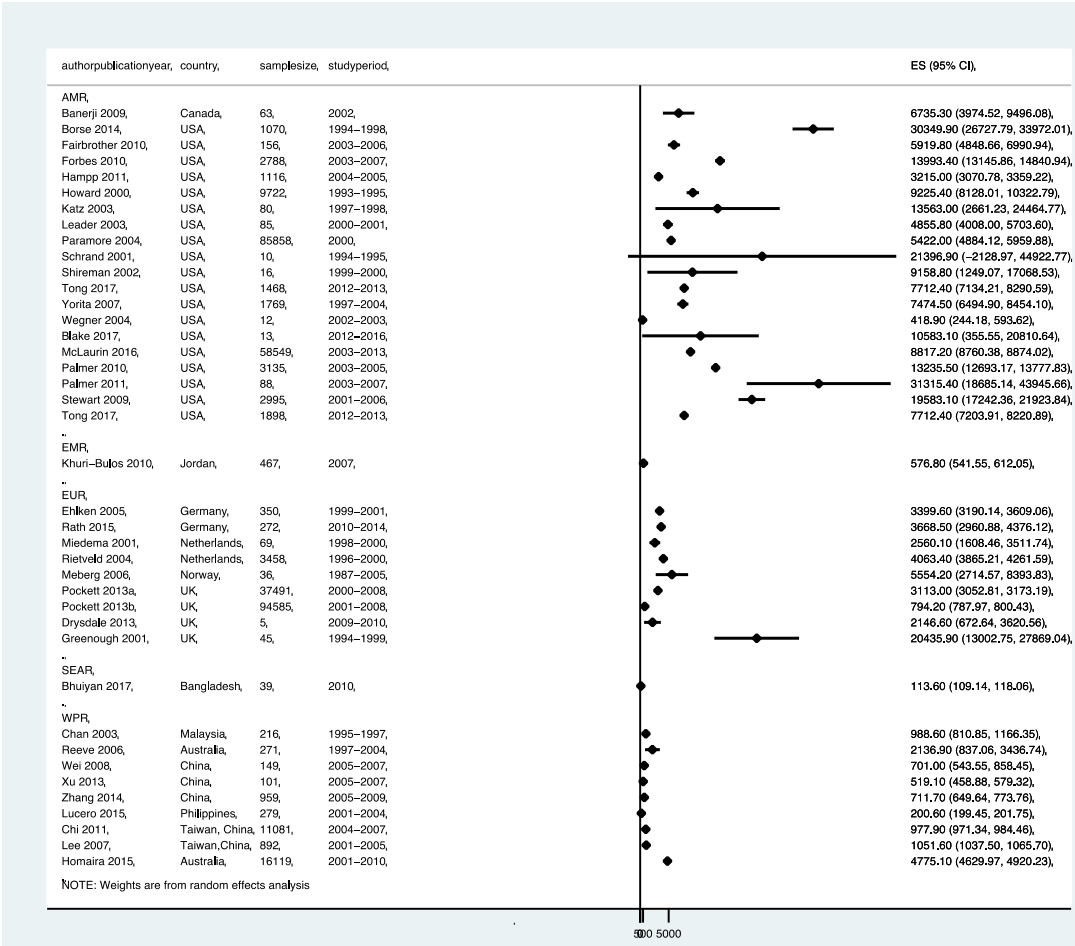

Figure 2. Cost per episode for inpatient management by WHO region (online)

Legend; EUR: European Region, AMR: Region of The Americas, WPR: Western Pacific Region, SEAR: South East Asia Region; EMR: Eastern Mediterranean Region.